IN THE UNITED STATES DISTRICT COURT FOR THE
MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

RUTH SMITH, Individually and as Widow for the Use and Benefit of Herself and the Next of Kin of RICHARD SMITH, Deceased,	)	Case #: 3:05-00444
	)	Judge Trauger
Plaintiff,	)	
-against-	)	
PFIZER INC., PARKE-DAVIS, a division of Warner-Lambert Company and Warner-Lambert Company LLC, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY LLC and JOHN DOE(S) 1-10,	)	
Defendants.	)	

STATEMENT OF PLAINTIFF'S EXPERT, MICHAEL TRIMBLE, M.D., AS TO GENERAL CAUSATION, PURSUANT TO LOCAL RULE 39.01(c)(6)(c)

Introduction

Good morning, my name is Professor Michael Trimble. As you have heard, I am a Medical Doctor, and I am Professor Emeritus of Behavioral Neurology at the Institute of Neurology, Queen Square, London, England. I am here today to provide my opinion that Neurontin can cause suicidal behavior, and my opinion is given with a reasonable degree of medical and scientific certainty. I will go into great detail about the evidence concerning the areas that Mr. Lanier told you about in his opening statement including the following areas:

1. Gabapentin was developed as an Epilepsy drug.
2. Brain Neurotransmitters: What they are and how they work.
3. Serotonin in the Brain.
4. Gabapentin reduces serotonin in the brain.
5. Gabapentin works quickly in the brain.
6. Gabapentin and GABA in the Brain.
7. FDA Confirms Gabapentin can cause suicidal behavior.
8. Gabapentin was A cause of Richard Smith's suicide. [*specific causation*]

The bases of my opinions in this case come from my expertise on research and clinical prescription of anticonvulsants over many years and my knowledge of both neurology, that is study of the brain, and psychiatry, that is study of behavior. In order to fully understand the scientific bases upon which this case resides an intimate knowledge of neurology and psychiatry is essential. I have reviewed published medical literature regarding gabapentin and similar drugs with similar properties and qualities. I have also been able to review the Defendants' secret documents given to me only because of this lawsuit. I have been involved with this lawsuit since 2005, when I was requested by the Smith family's attorneys to review Pfizer's confidential corporate records regarding its anticonvulsant drug, gabapentin, and to investigate whether gabapentin can cause suicidal behavior.

1. Gabapentin was Developed as an Epilepsy Drug

Gabapentin was originally approved for sale by the United States Food & Drug Administration as a drug to treat epilepsy. In other words, it was to be used to help prevent seizures. Quite some years later in about 2002, Gabapentin was approved to treate a very limited type of nerve pain from "shingles". This nerve pain is also called post-herpetic neuralgia. Here in the United States the drug is not approved for any other use.

It is important that I tell you that before being consulted by the Smith family's attorneys, I was originally asked by Warner-Lambert in approximately 1995 to review whether gabapentin was causing psychiatric side effects in patients taking it. Remember, at that time, Gabapentin was only approved for the treatment of epilepsy. I advised Warner-Lambert that "anticonvulsant drugs influence the mental state" and "[t]he main adverse effect of anticonvulsants is the link between anticonvulsant drugs and depression."[1] I also drew attention to the fact that of the case reports sent to me 36% (9 out of 21) of those which were related to aggression were likely related to the prescription of gabapentin and I warned against the provocation of aggression. Warner-Lambert at that time did not tell me that the FDA had told them to monitor for depression and suicide attempts as side effects of the drug in patients treated with gabapentin. This was in in 1992 - three years before they asked me for my opinions.

In 1995, I told Warner-Lambert that gabapentin may have been related to at least 9 of the 33 cases of behavior problems they asked me to review.

The drug company never told me in the mid-1990's when I was asked to evaluate the effects of Gabapentin, the FDA had already voiced their concern to them about Gabapentin increasing the risk of depression and suicide during the FDA's original clinical review. They never told me the FDA warned them that for users of Gabapentin that "depression, while it may not be an infrequent occurrence in the epileptic population, may become worse…or lead to suicide as it has resulted in some suicidal attempts" during clinical trials. I certainly would have wanted to know this at that time.

[1] Trimble, General Causation Decl. at p.28; Pfizer_PSUR_0002000 at 2005.

Also, during the drug company's human clinical trials of Gabapentin in the early 1990's, several patients became seriously depressed and some attempted suicide. They did not tell me that the drug company's own investigators considered several of the patients who reported severe depression or attempted suicide after taking Gabapentin was possibly or probably caused by Gabapentin. Fortunately during the original clinical trials that were conducted before Gabapentin was approved for sale, those patients were being closely monitored and several were taken off Gabapentin and given anti-depressants.

Ten years after my report for Warner Lambert, the Smith family lawyers consulted me and requested me specifically investigate if gabapentin was related to the death by suicide of . Because of the lawsuit, I was provided with research findings from the Defendants' files that I had not previously seen and had been kept secret.

I have also reviewed published medical articles and FDA reports on gabapentin. I have read transcripts of witness testimony from Pfizer witnesses, the Smith family, Mr. Smith's doctors, and other witnesses who have provided testimony in this case before this trial ever started.

Before today, I too have personally provided testimony under oath to Pfizer's lawyers at depositions, and I have provided testimony in Court - very much as I am doing today -to explain my opinion that gabapentin through is chemical actions on the brain increase a person's risk of suicidality. My opinions in this case were also set forth in writing and provided as reports to Pfizer's lawyers and the Court.

The Smith family's attorneys have paid me on a time basis of $500 an hour for paid me for my time doing work on this case.

2. Brain Neurotransmitters: What they are and how they work.

Lets consider the first area I discussed earlier: Brain Neurotransmitters - What they are and how they work. Neurotransmitters carry messages from one brain cell to another increasing or decreasing the energy or activity in groups of cells. One of these neurotransmitters, delivering energy to cells is serotonin. It has been known for a long time that serotonin is very important for the regulation of our mood states, and it alters mood by altering the energy in those areas of the brain that it sends the messages to. When the amount of serotonin in the brain falls then this leads not only in people who are psychiatrically unwell but also in people like you and I to have a decrease in their mood.

3. GABA and Serotonin in the Brain.

My opinion in this case is that gabapentin affects certain neurotransmitters in the brain that control mood and behavior. The effect of gabapentin on these neurotransmitters can cause depression and suicide.

So, for example, there are drugs that can either increase or decrease the amount of serotonin in the brain. Gabapentin is a drug that reduces the amount of serotonin, and the relevance of this is to remind you that decreasing serotonin in the brain is directly linked with suicidal behaviours This is one of the most replicated findings in the field of biological psychiatry.

People with low levels of serotonin get sad and depressed and some of these folks commit suicide. Now, not everybody who takes the drug kills themselves; the drug pushes people who might or might not kill themselves over the cliff. With a reasonable degree of medical and scientific certainty, I will show that taking Gabapentin can increase a person's risk of suicidality.

It is well known that these neurotransmitters play an important role in regulating a person's mood and behavior. For example, a decrease or imbalance in brain Serotonin or Norepinephrine is linked with depression and suicidality. As I will explain soon, in the case of Gabapentin, we have scientific, reliable evidence proving that Gabapentin alters the release of these chemical messengers – these neurotransmitters. Confidential corporate documents recovered in this lawsuit prove this to be the case.

But let me get back to my explanation of the scientific evidence demonstrating that a reduction or imbalance of the release of these neurotransmitters in the brain can lead to psychiatric disturbances, including depression and suicidal behavior.

There are numerous studies linking serotonin, dopamine and norepinephrine to a person's mental state, including depression and suicidal behavior. The evidence has been published in reliable medical texts and journals for decades.

Referenced Texts/Journals

The bases for my opinions is my own clinical research and experience as well as my reliance upon these medical texts and journals that span over 20 years and which validate my opinion that an imbalance in these brain neurotransmitters is related to mood disturbances and suicidal behavior.

While I cannot possibly list them all, the reference list you see here shows how this opinion spans decades of sources from the medical community:

Exhibit: References span > 20 years

1.	American Psychiatric Association's Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors. 2nd Edition. (2004)
2.	Trimble's Biological Psychiatry, 2d Edition (1996).
3.	Brown and Linoila's article titled, Serotonin metabolite studies in depression, impulsivity and violence, in Journal of Clinical Psychiatry (1990).

4.	Asberg and Shalling's article titled, Psychobiology of suicide, impulsivity and related phenomena. In the textbook Psychopharmacology: Third Generation of Progress (1987).
5.	Mayeux, Stern and Williams article titled, Altered serotonin metabolism in depressed patients with Parkinson's disease, in Journal of Neurology (1984).

Again, the list I can provide to you is far more extensive than what I have recited, but my point was simply to show you that the relationship between neurotransmitters and suicidal behavior has been an area of extensive research for a long time. My opinion in this litigation is not new or novel.

Exhibit 2067

Some drugs sold in the United States as anti-depressants specifically work by increasing serotonin in the brain. These drugs are referred to as Selective Serotonin Re-uptake inhibitors[2] (SSRIs). The best known of these is the antidepressant Prozac. However, these drugs, including Pfizer's own Zoloft. As the name SSRI explains, these drugs raise the level and activity of serotonin in the brain.

A clearer explanation can be shown to you by looking at this advertisement for Pfizer's Zoloft. This drug used to treat depression, and their description illustrates the simple point that, even the Defendants should not dispute, that a decrease in brain serotonin is related to depression. Here is what Pfizer advertises to you on its public website about depression and serotonin, which I can now read to you:

> "Because it is linked with so many functions in our body, serotonin has an effect on a wide range of conditions such as depression. This tie between depression and serotonin led scientists to an interesting find. Scientists believe people with depression could have an imbalance of serotonin in their brain. That means the level of serotonin is 'off'. So the nerve cells cant communicate or send messages to each other the right way. This lack of contact between cells might cause depression."

Exhibit:
Deposition Testimony of Defendants' employee/neuropharmacologist
Leslie Tive, PhD

But obviously, the Defendant's website is not the only place where there is evidence that a decrease or imbalance in neurotransmitters can lead to depression or suicidality. There is for example the deposition testimony from the Defendant's employee and neuropharmacologist, Dr. Leslie Tive, who has testified under oath that an imbalance in serotonin ---- either an increase or decrease ---- can be associated with depression. Lets

[2] See Trimble, General Causation Decl., at p.12.

look specifically at her deposition testimony transcript, but before just note that serotonin is one of several neurotransmitter messengers that have been linked to depression which are referred to as monoamines*: (read transcript or play audio/video)*

Q. Miss Tive, do you have an understanding as to whether an increased amount of serotonin or a decreased amount of serotonin in the brain can be associated with depression?
A. An increase or decrease of serotonin in the brain can be associated with depression. But when you talk about depression, are we talking about central nervous system depression, or are we talking about clinical depression?
Q. Let's talk about clinical depression. All right. What happens when there's a reduction in the flow of monoamines such as dopamine, serotonin, and norepinephrine?
A. You're saying monoamines in general?
Q. Correct.
A. A reduction in monoamines has been associated with depression.

So from this I will show you that since gabapentin decreases serotonin, in addition to other monoamines namely nor-epinephrine and dopamine, this leads to depression which increases the risk of suicide.

4. Gabapentin Reduces Serotonin in the Brain.

Exhibit 4765

This is Exhibit 4765. It is a confidential Research Report from May 1984. The title of the investigation is "Gabapentin attenuates the release of Noradrenaline and Serotonin, but not acetycholine, from brain slices." This animal study showed that gabapentin reduced the amount of serotonin and noradrenaline in the brain.

It is one of several studies I could quote leading to the same conclusions. What these scientists did was stimulated brain tissue of animal brain specimens in an attempt to replicate or mimic what may be happening in the brain of somebody with conditions such as epilepsy or pain.

Studies such as this were set up to examine what happens in brain cells when gabapentin is given, and part of the purpose was to see if gabapentin decreased the activity of brain cells which in clinical conditions are over active. Over activity of brain cells has been shown in epilepsy, but also in people with depression.

Exhibit 5310

Next I would like you to see Exhibit 5310. Charles Taylor did this study. He is a specialist in animal studies, he has worked for Pfizer on gabapentin for a long time, and he is actually now their hired expert.

At page 0008911 you can see that he writes about "Neurotransmitter Release": "Gabapentin has been known for many years to subtly reduce neurotransmitter release in vitro." That means in animal brain studies. "In particular, the release of tritiated noradrenaline, dopamine and serotonin have been studied, and there are reproducible decreases caused by gabapentin." In other words he agrees that there are many different studies that have found the same thing: Gabapentin reduced the amount of serotonin in the brain.

Exhibit 5354

Next, let us look at Exhibit 5354. When Pfizer or any other company conducts a research study, it sends the doctors who are running the study information on how the drug works. This is called a confidential Investigator Brochure. In 2004 the brochure told doctors doing studies that gabapentin decreased the amount of neurotransmitters in the brain. Next I will show you some of the published medical research that also shows that gabapentin reduces neurotransmitters.

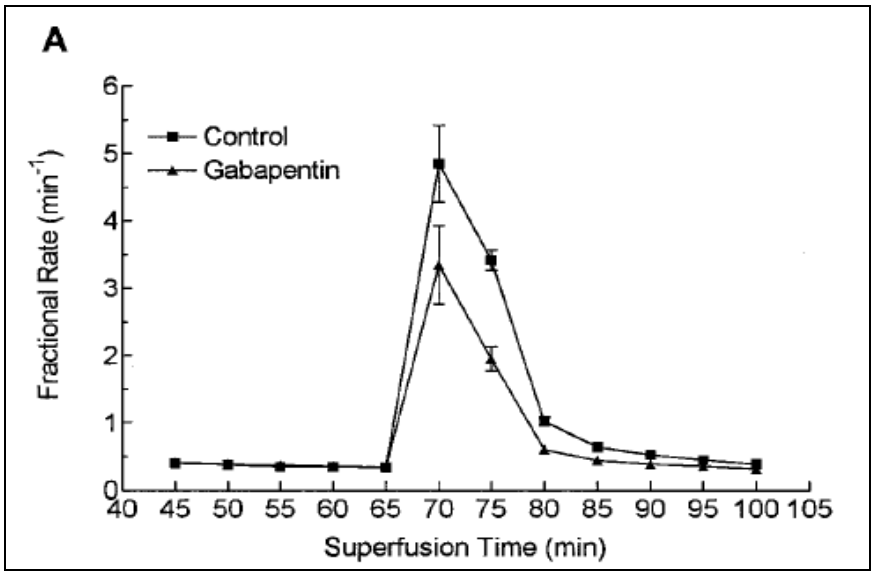
Dooley, et. al,
Stimulus-Dependent Modulation of [^{3}H]Norepinephrine Release from Rat Neocortical Slices by Gabapentin and Pregabalin
Journal of Pharmacology and Experimental Therapeutics (2000)

Pfizer's own scientists in the year 2000 published a paper in the highly reputable Journal of Pharmacology and Experimental Therapeutics. The article is entitled, ***Stimulus-Dependent Modulation of [^{3}H]Norepinephrine Release from Rat Neocortical Slices by Gabapentin and Pregabalin.*** You can see that the authors were from the Dept. of Neuroscience Therapeutics, Pfizer Global Research & Development.

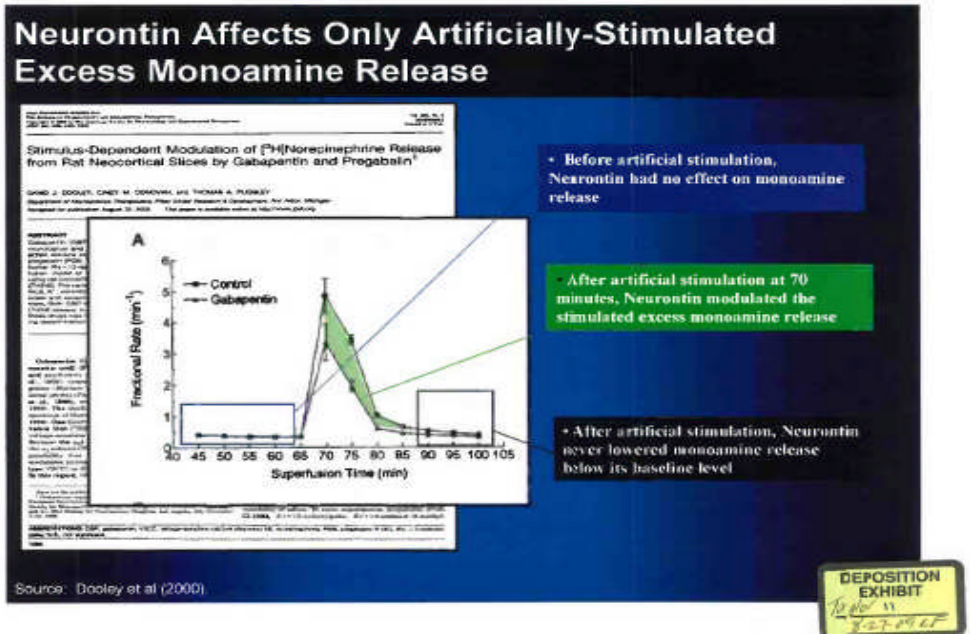
This study again confirmed that gabapentin reduces the release of neurotransmitters in the brain. This particular journal article has a useful chart that reflects the decrease in the release of monamine norepinephrine .

Figure 3 (A), as you can see is a chart that has a horizontal line which reflects the "Time" of gabapentin's effects on rats brain.., and a vertical line to reflect the increase or decrease in the effect on norepinephrine in the brain. This is where you see the term

"Fractional Rate".



(Alternative Demonstrative of Chart)



You can clearly see a significant decrease that begins between 65 and 70 minutes and continues almost to 100 minutes.

<u>Exhibit:</u>
Grame J Sills
The Mechanism of action of gabapentin and pregabalin
<u>Current Opinion in Phamacology (2006)</u>

In this article by the scientist Grame Sills, titled, "The Mechanism of action of gabapentin and pregablin," The author is referring to Gabapentin, and pregabalin which is a newer but similar drug manufactured by the Defendants' marketed as, Lyrica. In their review of gabapentin's mechanism of action, the authors referenced over a decade of research and literature on gabapentin. They concluded that gabapentin "reduced neurotransmitter release" and that this was a "biologically plausible mechanism . . . consistently observed at therapeutically relevant concentrations in pre-clinical studies…."

We are all obviously aware that animals are different from people, but that these animal tests are done for a reason. There are many similarities animal brains and human brains and animla studies help scientists learn about how drugs may help or hurt people. Whichever animal model is used, siceintists rely on such studies to research and develop the very medications that are used every day.

The animal models used in the investigations described above, were obviously considered of importance to clinical effects and there is no reason to believe that the same things that happen to the brains of animals should also not happen to the brains of people.

Exhibit:
Brawek B., and Dooley, et al.,
Differential modulation of K+-evoked 3H-neurotransmitter release from human neocortex by gabapentin and pregabalin,
Naunyn-Schmiedeberg's Arch Pharmacol (2008).

A recent publication in 2008 further validated the effects of gabapentin in human brain tissue – not just in animals. The article was co-authored by a Pfizer's research scientist, David Dooley, and it is titled "Differential modulation of K+-evoked 3H-neurotransmitter release from human neocortex by gabapentin and pregabalin".

In this study gabapentin was shown to decrease the release of serotonin and norepinephrine between 22% and 56%. In other words the same effects of gabapentin are noted whether human or rat brains are studied. The concentration levels of the drug used was similar to clinical plasma levels, in other words levels expected in the brains of humans taking the drug.

5. Gabapentin Works Quickly in the Brain

Exhibit:
Epilepsia. 2000 Jun;41(6):675-80.
Effects of gabapentin on brain GABA, homocarnosine, and pyrrolidinone in epilepsy patients.

Petroff OA, Hyder F, Rothman DL, Mattson RH.
Department of Neurology, Yale University, New Haven, Connecticut, USA.
"Gabapentin in human subjects increases brain GABA levels within an hour of taking the drug".

When one turns to human studies, the Petroff group at Yale University reported in a medical journal article, and I agree with these findings, that within one hour after taking gabapentin a clear increase in GABA levels in the brain was found. What this tells us is that within one hour, gabapentin begins altering the brain chemistry which, after a period of time, results in the decrease in the release of serotonin ultimately potentially leading to negative effects on mood.

Exhibit:

Seizure frequency and CSF parameters in a double-blind placebo controlled trial of gabapentin in patients with intractable complex partial seizures

Elinor Ben-Menachem [a,*], Birgitta Söderfelt [b], Anders Hamberger [c], Tomas Hedner [d], Lennart I. Persson [a]

[a] *Department of Neurology, University of Göteborg, Göteborg, Sweden*
[b] *Department of Neurology, Linköpings University, Linköping, Sweden*
[c] *Department of Histology, University of Göteborg, Göteborg, Sweden*
[d] *Department of Pharmacology, University of Göteborg, Göteborg, Sweden*

Received 10 October 1994; revised 16 March 1995; accepted 2 April 1995

When studying the effect gabapentin has on the seizure frequency of human patients, Elinor Ben-Menachem and her colleagues measured the effect gabapentin has on serotonin after three months of gabapentin treatment. While number of people in the study was not large enough to carry out meaningful statistics, it can bee seen that there is an approximately 40% reduction of serotonin after three months. What I find most important, however, is not ONLY the quantity of reduction, but rather the direction of the measured serotonin was lower, as expected.

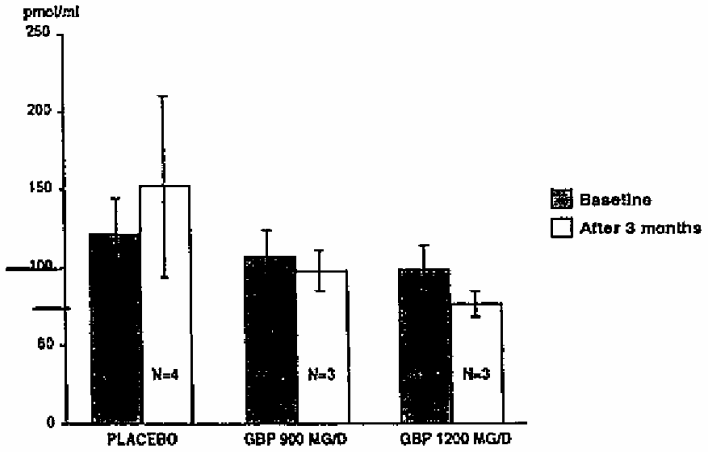


Fig. 5. 5-HIAA levels before and after 3 months treatment (mean ± S.E.M.).

6. Gabapentin and GABA in the Brain

Exhibit 2006

I am obviously not the only person addressing this question about the risks and benefits of gabapentin. You should know that Defendant's own employee – a Psychiatrist – Dr. Doug Feltner – emailed the Defendant's animal research scientist, Dr. CharlesTaylor, in October 2003 on this issue of how gabapentin could affect people, in a good and bad way. Lets take a look at that email. Dr. Feltner states the following question:

> "I suppose the question is: what are the consequences of the increases in GABA in human brain that are caused by gabapentin? It strikes me that they might contribute to efficacy and adverse events in humans."

Why is this an important document? This confidential email from one Pfizer scientist to another is confirmation of the company's awareness that gabapentin affects the human brain in both good and bad ways. The "efficacy" is the good, and the "adverse events" are clearly the bad.

We can look outside of Pfizer's confidential corporate documents to find further evidence about the effect of gabapentin the brain's neurotransmitters.

Bettina Schmitz, Effects of Antiepileptic Drugs on Mood and Behavior
47 Epilepsia (Supplement 2) 28-33 (2006)

A 2006 Journal article in Epilepsia discussed the risks and benefits of gabapentin's along with several other anticonvulsant drugs. The title of the article by Dr. Bettina Schmitz is

"Effects of Antiepileptic Drugs on Mood and Behavior". This peer reviewed journal accepted as a reliable source of information regarding anticonvulsant drugs.I think its important to mention to you that I have also co-authored medical literature with Dr. Schmitz in the past, and I am included on her list of "references" in this particular journal article at least 7 times.

Dr. Schmitz discusses that "mechanisms of drug-induced psychiatric changes" include "GABAergic effects in depression." Now, I certainly agree as does Dr. Schmitz in her article that anticonvulsants have their benefits. These are important drugs to be considered by well informed doctors and patients. Take a look at this chart from her article at page 31:

TABLE 1. *Two categories of AED with different psychotropic effects depending on the preexisting mental state (40)*

Mechanism	GABA-ergic drugs	Antiglutamatergic drugs
Psychotropic effects	Sedating, anxiolytic, depressogenic, antimanic	Activating, anxiogenic, antidepressive
Drugs	Barbiturates, benzodiazepines, valproate, vigabatrin, tiagabine, gabapentin	Felbamate, lamotrigine
Effect in activated patients	Positive	Negative
Effect in sedated patients	Negative	Positive

Here, we see that gabapentin is included in the group of GABAergic drugs with a "Mechanism" that has "Psychotropic effects" which are "depressogenic". This is essentially my opinion in this case for over the years.

You will see that this table makes reference to GABAergic drugs. I had mentioned to you earlier that several neurotransmitters were related to the control of mood and that in addition to monoamines such as serotonin another neurotransmitter messenger GABA is involved. The crucial link here is to understand that drugs which increase GABA in the central nervous system decrease serotonin and that there are human studies using very sophisticated methods of imaging these neurochemical messengers in the brain which have shown that gabapentin increases brain GABA. There is further evidence from human studies using sophisticated brain stimulation techniques that support these views, and there is evidence in human studies that gabapentin alters the release of serotonin in the brain in ways which predict a decrease in serotonin with chronic doses.

I have had my attention drawn to the fact that there are several other ways of

increasing GABA that might imply that increasing GABA in the human brain is antidepressant. There are many ways of increasing GABA, since it is one of the commonest neurotransmitters in the brain. However, there is a world of difference between increasing it physiologically (by movement – as with yoga) and increasing it artificially by applying external agents such as drugs. The former is a part of normal brain functioning, while the latter sets up an abnormal situation for the brain's neurochemistry. It is the case that some antidepressants have been shown to increase GABA (some SSRI's), but these drugs too have been associated with release of aggression and suicidality.

To reinforce my point then that while there is clearly debate between myself and the Defendants, there is reliable peer reviewed evidence in the scientific community that gabapentin is potentially associated with depression and that the most likely mechanism is through decreasing serotonin in the brain. There are plausible explanations for this including its effect on increasing GABA in the brain.

7. FDA Confirms Gabapentin can cause suicidal behavior

Pharmacoepidemiology Studies Validate My Opinion that Gabapentin Can Cause Suicidality

In addition to these experimental animal and human studies it is important to consider epidemiological data, in other words figures obtained from larger populations of patients on the side effects of gabapentin.

Exhibit 3849
U.S. FDA Alert on Anticonvulsants and Suicidality

Lets look at Exhibit 3849. In January 2008, the United States Food & Drug Administration issued a nationwide safety alert after reviewing and analyzing clinical trials from 11 anti-convulsant drugs, including gabapentin (its brand name being Neurontin).

The FDA analysis indicated that "Patients taking antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation compared to patients receiving a placebo."

Now, because there was not necessarily enough data for each of the 11 drugs to be examined on their own, the FDA reviewed the 11 anticonvulsant drugs in a way that is called a meta-analysis. Simply imagine a cake or pie in which there are 11 slices. While each slice of the pie may not be enough on its own to make a decision, the FDA had the benefit of all 11 slices – an entire pie.

This analysis allows the FDA to review 11 anticonvulsants to determine if there is a common result that can be applied to all the drugs in the analysis.

Exhibit 2808
FDA Statistical Review & Evaluation 2008

On May 23, 2008, the FDA released its Statistical Review and Evaluation of the meta-analysis. The FDA concluded as follows:

> "In conclusion, antiepileptic drugs are associated with increased risk of suicidality relative to placebo in randomized placebo controlled trials. The effect appears consistent among the group of 11 drugs."

The FDA conducted an Advisory Committee in July 2008, at which time it invited over 20 scientists and medical professionals from across the United States. The Committee was asked to vote their decision on whether the increased risk of suicidality applied to all the anticonvulsants studied in their analysis.

Their vote was YES, 20 votes to 0, with one member who abstained (and did not vote).

I am not an expert in epidemiology. However, I consider the FDA's findings of considerable importance along with the statements of the Advisory Committee regarding the association between anti-epileptic drugs and suicidality.

Since the FDA's decision, other research scientists have carried out studies examining the link between antiepileptic drugs and suicide.

One of Defendants' experts, Robert Gibbons, published an article in the Archives of General Psychiatry in 2009. His conclusion was that, despite Food and Drug Administration reports regarding increased risk of suicidality, he did not find an increased risk of suicide attempts in patients with bipolar disorder who took anticonvulsants.

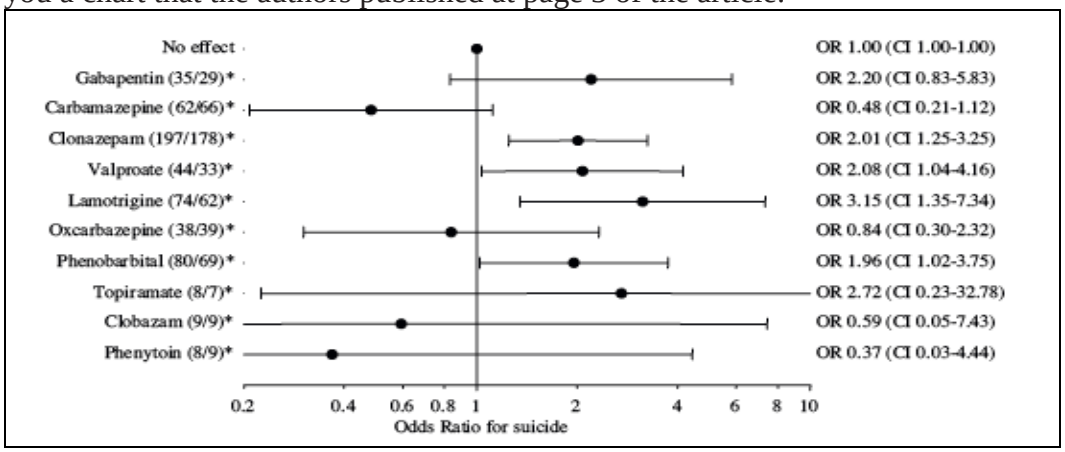
Unfortunately this study did not consider completed suicide.

Exhibit:
Antiepileptic drugs and risk of suicide: a nationwide study
in Pharmacoepidemiology and Drug Safety (March 2010)

But more recent articles written by authors that have nothing to do with this litigation have supported the actions and opinions of the FDA. For example, in March 2010, the Journal of Pharmaco-epidemiology and Drug Safety published a study titled, "Antiepileptic drugs and risk of suicide: a nationwide study". The authors studied a population group of 169,725 patients, of which 52,203 were receiving gabapentin patients.

The authors stated (at page 4) that the result of their study "showed a trend towards lowered risk associated with the usage of carbamazepine and an increased risk with the usage of gabapentin."

To demonstrate this "trend" of an increased risk with use of gabapentin, let me show to you a chart that the authors published at page 3 of the article:



This is "Figure 1" in the article. You can see the vertical line in the middle as the point to determine if there is a risk of suicide with a drug studied in the article. Now look at each drug and you can see a black dot or point that reflects the drug's dds Ratio for suicide. By Odds Ration they are referring to the amount of increased risk . If a black dot or point is to the right side of the vertical line, then it can be said to have a "trend" towards increasing risk of suicide.

For our purposes, lets look at gabapentin. It is the first drug listed at the top left corner. The Odds Ratio for Suicide is listed as 2.20. You can see that the black dot or point is at the 2.20 mark. There is also a corresponding range for each black dot or point in the chart. Because the range of the Odds Ratio also crosses to the left side of the vertical line, the risk is not considered "statistically significant" for gabapentin. However, it is evidence of a "trend" towards increasing the risk. For illustrative purposes, take a look at Carbamazepine – it's the second drug listed – and it has a black dot to the left of the vertical line. This means the trend is for a decrease the risk of suicide.

Lets put aside the statistics for a moment and let me return to neurotransmitters. These authors of this article explained (at page 6) that gabapentin increased GABA levels resulting in decreased release of neurotransmitters. Here is exactly what they said:

> "Furthermore, phenobarbital, clonazepam, clobazam, valproate, gabapentin and tiagabine elevate gamma-aminobutyric acid (GABA) levels and potentiate the GABA-mediated inhibitory neurotransmission response, whereas levetiracetam reduce GABA levels."

Exhibit:
Patorno, E., et al.,
Anticonvulsant Medication and the Risk of Suicide, Attempted Suicide, or Violent Death,
JAMA (April 14, 2010)

In April 2010, the Journal of American Medical Association published an article titled, "Anticonvulsant Medication and the Risk of Suicide, Attempted Suicide, or Violent Death". As you can see and read, the authors had an "objective": These authors set out "to evaluate the risk of suicidal acts and combined suicidal acts or violent death associated with individual anticonvulsants."

The authors in stated (at page 1406) that with respect to gabapentin, "the risk of attempted or completed suicide was meaningfully increased for gabapentin. Similar to the previous article's Odds Ratio these authors determined a "hazard ratio" of 1.42. So you must imagine that the black dot or point in this case would be to the RIGHT of the vertical line we discussed earlier. In fact, these authors in their study found the risk to be statistically significant.

So, what can we take away from these epidemiology statistics regarding gabapentin: we can say that we have scientific, reliable evidence that is consistent with my opinion that gabapentin can cause depression and suicidal behavior.

While the authors for the JAMA article stated at page 1408 that anticonvulsants have psychotropic effects, including mood and behavior changes they also say there is "no clear understanding of a mechanism of action that could lead to suicidal behavior." In my view this perhaps reflects on the authors' lack of knowledge of the relationship between these drugs, brain neurochemistry and the links between neurochemistry and suicidal behaviours. Although t hey recognize that gabapentin has been "associated with behavioral problems such as aggression and hyperactivity…", they simply may not be aware of the information I have provided for you on these important associations.

8. Gabapentin was A Cause of Richard Smith's Suicide

[Refer to Specific-Causation Statement]

In conclusion, my opinions in this lawsuit are given to you with a reasonable degree of medical and scientific certainty. They are as follows:

1. Gabapentin is a strong mind altering drug that works within an hour or so by changing a persons brain chemistry;

2. Gabapentin can cause people who ingest it to become depressed and suicidal;

3. Gabapentin is a drug which increases the activity of GABA in the central nervous system. This is but one mechanism whereby gabapentin decreases the release of

important neurotransmitters in the brain, particularly serotonin. Decreasing serotonin is intimately linked with depression, aggressivity and suicidal acts. Gabapentin on the balance of probability and on the basis of the scientific and clinical data can cause depression and suicidality in people who take this drug.

4.[*specific causation*] Gabapentin was A substantial factor in causing Mr. Smith to commit suicide.

I am hopeful that I have explained my opinion and the bases of my opinion regarding Neurontin to you in a way that is clear and which details the areas that Mr. Lanier told you about in his opening statement including the following areas:

1. Gabapentin was developed as an Epilepsy drug.
2. Brain Neurotransmitters: What they are and how they work.
3. Serotonin in the Brain.
4. Gabapentin reduces serotonin in the brain.
5. Gabapentin works quickly in the brain.
6. Gabapentin and GABA in the Brain.
7. FDA Confirms Gabapentin can cause suicidal behavior.
8. Gabapentin was A cause of Richard Smith's suicide. [*specific causation*]

If the Court allows, I would welcome the opportunity to address any questions you or the Court may have. Thank you.